1. FINAL PUBLISHABLE SUMMARY REPORT

Summary of Progress

Retinal processing in known to change during different ambient light conditions. In particular, the different photoreceptor dominate the transformation of light energy into neural signals. Rods operate at low light levels, while cones dominate during daylight conditions. Aside from the use of different photoreceptors the receptive field properties of retinal ganglion cells, the output of the retina, are known to change with the ambient light level. In particular the cells selectivity for different spatial frequencies. During this project we have uncovered a neural circuit capable of switching on the inhibitory surround of a neuron in a input state dependent manner. Specifically, we have been able to describe the circuitry that mediates the break down of the center-surround receptive field organization of retinal ganglion cells in scotopic conditions. Using a combination of two-photon microscopy and a mouse expressing a florescent protein (EYFP) in a subset of its ganglion cells we performed targeted recordings from a large ON ganglion cell type, termed PV1 (Figure 1). The spatial receptive field properties were explored using spots and annuli of different sizes presented at background light intensities that stimulated only rods, both rods and cones or only cones . Similar to studies by Kuffler and Barlow in the 1950s, we found that the PV1 cell has no surround for stimuli that activated only rods, while for light levels that stimulated cones the PV1 cell exhibits clear center-surround antagonism. This results in the specific suppression of the cells response to the presentation of large spots while the response of smaller spots remain unaffected. Surprisingly the appearance of the surround was not graded but abrupt and switch-like, appearing

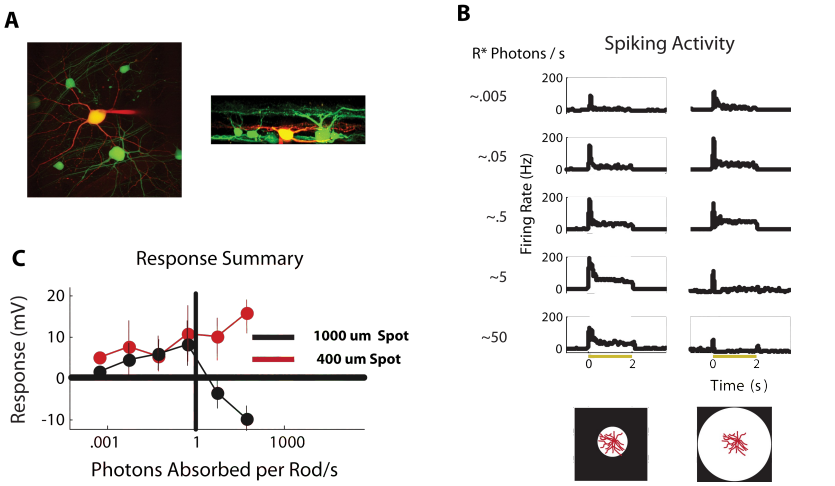

Figure 1: Switch-like Activation of Inhibitory Surround. A. Two-photon images of the PV1 cell filled with a red fluorescent dye in the PVCre x ThyStpY YFP mouse retina. **B.** Example recording illustrating the affect of activating the inhibitory surround of the cell. **C.** Summary of how activating the surround of the cell specifically affects the presentation of one stimuli,1000 um spot, and not the other, the 400 um spot.

with full effectiveness in less then 15 s.

Having identified this robust phenomenon we turned our attention to the responsible circuitry. As a first step we recorded from different circuit components in the retina that mediated either scotopic or photopic vision, i.e. the rod and cone pathways respectively. We performed recording from both rod and cone bipolar cells in slice preparation of the retina. We found that the threshold for ON cone bipolar cells was identical to the light level at which we begin to see the affect of inhibition in the PV1 cell. Illustrating that the light level at which inhibition appears corresponds with the threshold of cones activation.

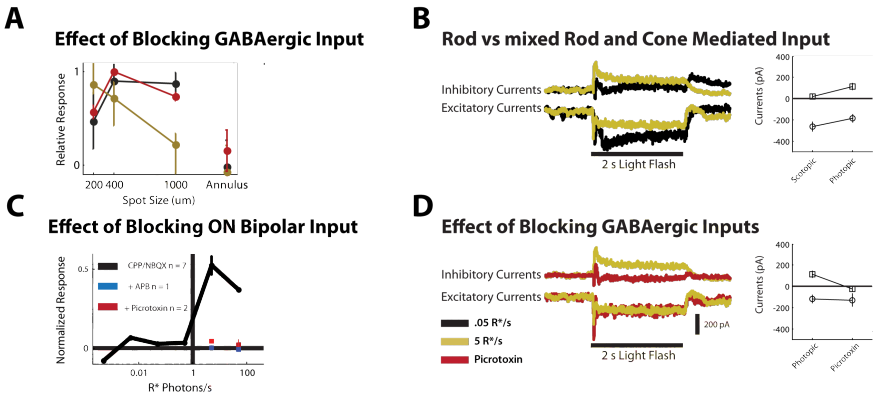

Figure 2: Circuit Elements Mediating Activation of Inhibitory Surround. A. The application of the GABA antagonist picrotoxin abolishes the inhibuitory surround of the PV1 cell. **B.** The balance of excitation and inhibition shifts toward inhibition in photopic vs scotopic light conditions. **C.** The application of APB and picrotoxin block the inhibitory input to the PV1 cells. **D.** The application of picrotoxin selectively abolishes the inhibitory input to the cell.

In order to elucidate how the inhibitory surround is selectively activated by the cone pathway we used a combination of pharmacological manipulation and electrophysiological recordings. Voltage clamp experiments suggest that the inhibitory surround is mediated by postsynaptic inhibition from wide field spiking GABAergic amacrine cells. The application of the GABA antagonist picrotoxin and the sodium channel blocker tetrodotoxin, but not glycinergic antagonist strychnine strongly reduced the inhibitory currents while leaving the excitatory unaffected (Figure 2). Additionally GABAergic inhibition is only present at light levels bright enough to activate cones. Experiments It is mediated by ON cone bipolar cells as demonstrated by its sensitivity to the mGluR6 agonist, APB. Our work suggests a neural circuit switch that turns on a widefield GABAergic amacrine cell via electrical coupling with ON cone bipolar cells and is toggled by the activation of cones.